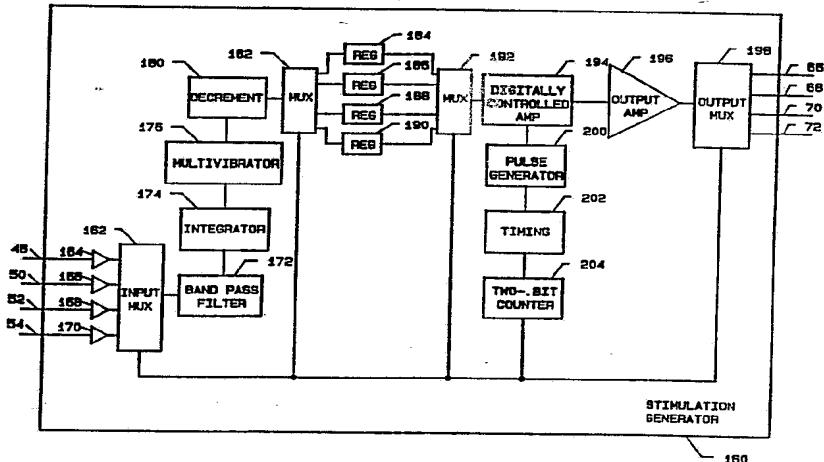




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US92/02391</p> <p>(22) International Filing Date: 24 March 1992 (24.03.92)</p> <p>(71) Applicant: MEDTRONIC, INC. [US/US]; 7000 Central Avenue N.E., Minneapolis, MN 55432 (US).</p> <p>(72) Inventor: KALLOK, Michael, J.; 2910 - 13th Terrace NW, New Brighton, MN 55112 (US).</p> <p>(74) Agent: LATHAM, Daniel, W.; Medtronic, Inc., 7000 Central Avenue N.E., Minneapolis, MN 55432 (US).</p> <p>(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).</p>			
			Published <i>With international search report.</i> <i>With amended claims.</i>

(54) Title: IMPROVING MUSCLE TONE



(57) Abstract

An apparatus for and a method of improving the muscle tone of a patient using chronic subthreshold electrical stimulation. For patients suffering from obstructive sleep apnea, for example, the muscles of the upper airway are stimulated to mitigate or prevent the adverse medical condition, caused, in part, by excessively flaccid muscle tissue around and in the airway. A stimulation generator (160) supplies pulses to the muscle to be treated through insulated leads (66-72), which are coupled to electrodes directly in contact with the appropriate neuromuscular tissue. The output of the stimulation generator is adjusted to an amplitude of sufficiently low level as to prevent fused tetanic contraction of the stimulated muscle. The adjustment may be made manually or automatically using electrodes to sense the tension of the stimulated muscle. In the automatic mode, the sensing system insures the stimulation level is decreased below the threshold of muscle tetanus. Stimulation may be accomplished at a particular site or may be multiplexed to a number of sites. Chronic stimulation will enhance muscle tone to an individual degree and then will simply maintain the desired status.

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IMPROVING MUSCLE TONECross Reference to Co-pending Applications

None.

BACKGROUND OF THE INVENTIONField of the Invention

5 The present invention generally relates to implantable medical devices, and more particularly, relates to implantable medical devices which provide subthreshold stimulation of muscle tissue.

10 Description of the Prior Art

The medical characteristics of sleep apnea have been known for some time. There are two generally recognized forms of the disease. The first is central sleep apnea which is associated with the failure of the body to automatically generate the neuromuscular stimulation necessary to initiate and control a respiratory cycle at the proper time. Work associated with employing electrical stimulation to treat this condition is discussed in "Diaphragm Pacing: Present Status", by William W. L. Glenn, in Pace, Volume I, at pages 357370 (July-September 1978).

The second condition is known as obstructive sleep apnea. It is discussed at some length in "Obstructive Sleep Apnea: Diagnosis and Treatment", by Drs. Cook and Osguthorpe in Journal of South Carolina Medical Association, 81 (12): 647 - 651 (December 1985). Additional references treating the subject include: "Physiologic Basis of Therapy for Sleep Apnea", by K. P. Strohl, N.S. Cherniack, and B. Gothe in American Review of Respiratory Disease, Volume 134, pp. 791-802 (1986); and "Obstructive Sleep Apnea Syndrome", by J. Kaplan and B.A. Staats in Mayo Clinic Proceedings, Volume

65, pp. 1087-1094 (1990).

Electrical stimulation of muscle tissue has been used for some time. Much work has been done in this area in cardiac pacing, for example. Paul E. Ciske and John A.

5 Faulkner in "Chronic Electrical Stimulation of Nongrafted and Grafted Skeletal Muscles in Rats", in Journal of Applied Physiology, Volume 59(5), pp. 1434-1439 (1985), discuss some physiological effects of chronic stimulation.

At present, a tracheostomy may be the treatment of
10 choice for a number of patients when obstructive sleep apnea is severe. However, some interest has been displayed in electrical stimulation of the muscle tissue along the upper airway during respiration. U.S. Patent No. 4,830,008 issued to Meer discusses a technique for electrical stimulation of
15 the muscles of the upper airway in synchrony with the respiratory cycle. U.S. Patent No. 4,506,666 issued to Durkan discusses such stimulation in conjunction with pressurized airflow supplied by a respirator. A similar approach is discussed by Miki et al., in "Effects of
20 Submental Electrical Stimulation During Sleep on Upper Airway Patency in Patients with Obstructive Sleep Apnea" in American Review of Respiratory Disease, Volume 140, pp. 1285-1289 (1989).

The electrical stimulation of the prior art techniques,
25 however, are primarily concerned with causing contractile motion of the stimulated muscle. This means that the stimulation energy must necessarily be relatively large and the effects of the stimulation are directly cognizable by the patient.

30

SUMMARY OF THE INVENTION

The present invention overcomes the disadvantages of the prior art by providing a method and technique for treating medical conditions, such as obstructive sleep
35 apnea, with subthreshold stimulation. This stimulation is

accomplished by pulses which have an insufficient amplitude, either individually or in combination, to cause direct contraction of the stimulated muscles. The result is an improvement in general muscle tone of the stimulated muscle
5 without use of excess stimulation energy and without undue sensory stimulation of the patient. It is this general tightening of the musculature which provides the relief to the patient with obstructive sleep apnea.

The stimulation pulses are supplied by a stimulation
10 generator coupled through insulated electrical leads to electrodes in contact with the tissue to be stimulated. The amplitude of the output pulses may be manually adjusted to prevent capture of the muscles to be stimulated.

Alternatively, the tension of the stimulated muscle
15 tissue may be sensed by the stimulation generator. Special electronic circuitry can detect the capture threshold and decrease the stimulation amplitude to prevent contraction.

The technique may be practiced by stimulation at one or more sites. To facilitate multiple site stimulation, the
20 output of the stimulation generator may be suitably demultiplexed.

BRIEF DESCRIPTION OF THE DRAWINGS

Other objects of the present invention and many of the
25 attendant advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, in which like reference numerals designate like parts
30 throughout the figures thereof and wherein:

FIG. 1a is a graphical representation of muscle tension with 10 hertz stimulation;

FIG. 1b is a graphical representation of muscle tension with 50 hertz stimulation;

35 FIG. 1c is a graphical representation of muscle tension

with 100 hertz stimulation;

FIG. 2 is a view showing a typical arrangement of stimulation and sensing electrodes;

FIG. 3 is a graphical representation of the sensed 5 muscle tension for stimulation pulses above and below the capture threshold;

FIG. 4 is a graphical representation of the stimulation outputs and integrated sensed inputs of a multiplexed subthreshold stimulation system;

10 FIG. 5 is a block diagram of a stimulation generator having multiplexed inputs and outputs; and,

FIG. 6 is a graphical representation of general muscle tone over time using chronic subthreshold stimulation.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. 1a is a graphical representation 10 of muscle tension 13 as a function of time 14 under subthreshold stimulation at a rate of 10 pulses per second. The response 20 produced is termed slow-twitch.

It can be seen that even though the tension produced tends to be cumulative, the relative peak associated with each stimulation pulse is prominently evident. As stimulation pulses 15a, 15b, 15c, 15e, 15f, 15g, 15h, 15i, and 15j cause 25 the subject muscle to twitch, relative peaks 11a, 11b, 11c, 11d, 11e, 11f, 11g, 11h, 11i, and 11j, respectively, are produced. Relative troughs 12a, 12b, 12c, 12d, 12e, 12f, 12g, 12h, 12i, and 12j, respectively, are the corresponding troughs 30 between stimulation pulses. Tension 16 is the level of tension required to produce contraction.

FIG. 1b is a graphical representation 17 of muscle tension 13 as a function of time 14 under subthreshold stimulation at a rate of 50 pulses per second. The term given to this reaction is non-fused tetanus. It can be seen that as 35 each of the stimulation pulses 18a-18n is generated, the

cumulative muscle response contains faintly pronounced relative maxima and minima.

FIG. 1c is a graphical representation 19 of a fused tetanus response of the subject muscle. The muscle tension 13 5 as a function of time 14 results in a smooth, cumulative curve. Stimulation pulses 20a-20n are produced at the rate of 100 per second. No relative maxima and minima are present at this stimulation rate.

FIG. 2 shows the typical arrangement 30 of stimulation 10 and sensing electrodes in a system having multiplexed inputs and outputs. Individual muscles 32, 34, 36, and 38 represent musculature of the upper airway in the obstructive sleep apnea patient. Typical muscle groups include genioglossus, thyrohyoid, sternohyoid, omohyoid, geniohyoid, mylohyoid, 15 hypoglossus, stylohyoid, etc.

Electrodes 40, 42, 44, and 46 are stab-in electrodes such as Medtronic Model 4951. Each is coupled to the stimulation generator (see also Fig. 5) by a different one of insulated leads 48, 50, 52, and 54, respectively.

20 Electrodes 56, 58, 60, and 62 electrically coupled to insulated leads 64, 66, 68, and 70, respectively, may be of similar design and construction. Each of electrodes 56, 58, 60, and 62 senses the tension of the corresponding muscle 32, 34, 36, and 38.

25 FIG. 3 is a graphical representation of stimulation pulses which are both greater than and less than the capture threshold, along with the corresponding tension signal as sensed and integrated. Stimulation amplitude consists of individual pulses 74, 76, 78, 80, 82, 84, 86, and 88. Each 30 has a pulse width of approximately one millisecond. Individual pulses 74, 76, 78, and 80 have a lesser amplitude than capture threshold 22, represented by curve 90. Similarly, each of the individual pulses 82, 84, 86, and 88 exceeds the amplitude of curve 90.

35 Curve 92 shows the tension signal as sensed from the

stimulated muscle and integrated into a smooth curve. The region prior to incline 94 represents the integrated tension signal with the subthreshold stimulation of individual pulses 74, 76, 78, and 80. The region of curve 92 between incline 94 and decline 96 is indicative of the integrated tension signal with individual pulses 82, 84, 86, and 88 sufficient to stimulate contraction.

FIG. 4 is a graphical representation of the operation of a multiplexed system having four separate inputs and outputs. 10 Curve 98 shows stimulation pulses 106, 108, 110, 112, 114, 116, 118, and 120 applied to a first stimulation electrode (see also Fig. 2).

Similarly, curves 100, 102, and 104 show the stimulation pulses applied to the second, third, and fourth stimulation 15 electrodes, respectively. Curve 154 shows the integrated time multiplexed tension signal from the corresponding sensing electrodes.

Stimulation pulses 106, 108, 110, and 112 each have an amplitude in excess of curve 98 representing the capture 20 threshold. Therefore, region 158 of curve 154 indicates capture, because it has an amplitude greater than sensing threshold 156. This data is used by the stimulation generator as explained in greater detail below to lower the amplitude of the stimulation pulses to the corresponding muscle tissue.

25 Stimulation pulses 124, 126, 128, and 130 are of a lower amplitude than capture threshold level 132. Similarly, pulses 134, 136, 138, and 140 and less than level 142, and pulses 144, 146, 148, and 150 are less than level 152.

FIG. 5 is a block diagram of stimulation generator 160 30 which supplies the stimulation pulses of Fig. 4 and also performs the sensing function. Sensing inputs are received from insulated leads 48, 50, 52, and 54, and stimulation pulses are output via insulated leads 66, 68, 70, and 72 (see also Fig. 2).

35 The individually sensed tension signals are amplified by

sense amplifiers 164, 166, 168, and 170, respectively. Input mux 162 time division multiplexes the signals in accordance with the output of recycling two-bit counter 204 which is driven by the ten millisecond output of timing 202.

5 In turn, each of the amplified tension signals is output from input mux 162 to band pass filter 172. The output of band pass filter 172 severely attenuates components over one megahertz. The output is integrated by integrator 174 to provide the smooth signal discussed above (see also curve 92
10 of Fig. 3). Multivibrator 176 thresholds this signal to determine if the sensed amplitude indicates capture as explained above. If yes, decrement 180 is enabled to decrement the corresponding one of registers 184, 186, 188, and 190 through mux 182. If no, decrement 180 is not enabled.

15 Mux 182 supplies the contents of the proper one of registers 184, 186, 188, and 190 to control the output of digitally controlled amp 194. This ensures that the corresponding stimulation pulses which are output will be subthreshold. The pulses are generated by pulse generator 200
20 based upon timing 202 which enables synchrony with the multiplexer activity. Output amplifier 196 is a linear amplifier which provides the proper output amplitude. Output mux 198 selects the proper stimulation electrode for the stimulation pulses.

25 FIG. 6 is a graphical representation 206 of the general muscle tone 210 as a function of the period of subthreshold stimulation 208. Note that following a subthreshold stimulation period 208, the general muscle tone does not appreciably increase and the continued subthreshold
30 stimulation serves to maintain the level of muscle tone.

Having thus described the preferred embodiments of the present invention, those of skill in the art will be readily able to appreciate the additional useful embodiments which may be utilized without departing from the scope of the claims
35 hereto attached.

I CLAIM:

1. A method of improving general tone of a muscle comprising:
 - a. electrically stimulating said muscle at an amplitude, frequency and pulse width;
 - b. determining whether said stimulating causes fused tetanic contractile activity of said muscle; and,
 - c. decreasing said amplitude of said electrically stimulating until said fused tetanic contractile activity ceases.
- 2 . A method according to claim 1 wherein said steps are repeated.
3. An apparatus comprising:
 - a. means for supplying stimulation to a muscle; and,
 - b. means coupled to said supplying means to ensure that said stimulation is subthreshold.

AMENDED CLAIMS

[received by the International Bureau on 22 December 1992 (22.12.92);
original claims 1-3 amended; new claims 5-12 added; (3 pages)]

1. A method of improving general tone of a muscle comprising:
 - a. electrically simulating said muscle at a first amplitude, frequency and pulse width;
 - b. determining whether said stimulating causes fused tetanic contractile activity of said muscle;
 - c. decreasing said frequency of said electrically simulating until said fused tetanic contractile activity ceases; and
 - d. continuing to stimulate said muscle at a subtetanic frequency with pulses having a second amplitude, frequency and pulse width to improve over all tone of said muscle.
2. A method according to claim 1 performing said steps at more than on site.
3. An apparatus comprising:
 - a. means for supplying stimulation to a muscle.
 - b. means coupled to said muscle for sensing tetanic contraction; and
 - c. means coupled to said supplying means and said sensing means for adjusting said stimulation in response to said sensing means to ensure that said stimulation is subtetanic.
4. An apparatus according to claim 3 wherein said adjusting means comprises means to cause said supplying means to decrease frequency of said stimulation to said muscle to ensure that said stimulation is sub-tetanic.
5. An apparatus according to claims 3 or 4 wherein said supplying means comprises means for stimulating a

plurality of locations of said muscle.

6. A method of treating obstructive sleep apnea comprising:

- a. coupling electrodes to muscle tissue of the upper airway; and
- b. chronically stimulating said muscle tissue at a stimulus level of less than that producing fused tetanic contraction.

7. A method according to claim 6 further comprising:

chronically monitoring said muscle tissue of said upper airway for occurrence of fused tetanic contraction.

8. A method according to claims 6 or 7 further comprising:

decreasing frequency of said stimulation of said muscle tissue if said chronically monitoring step indicates fused tetanic contraction.

9. An apparatus for treating obstructive sleep apnea comprising:

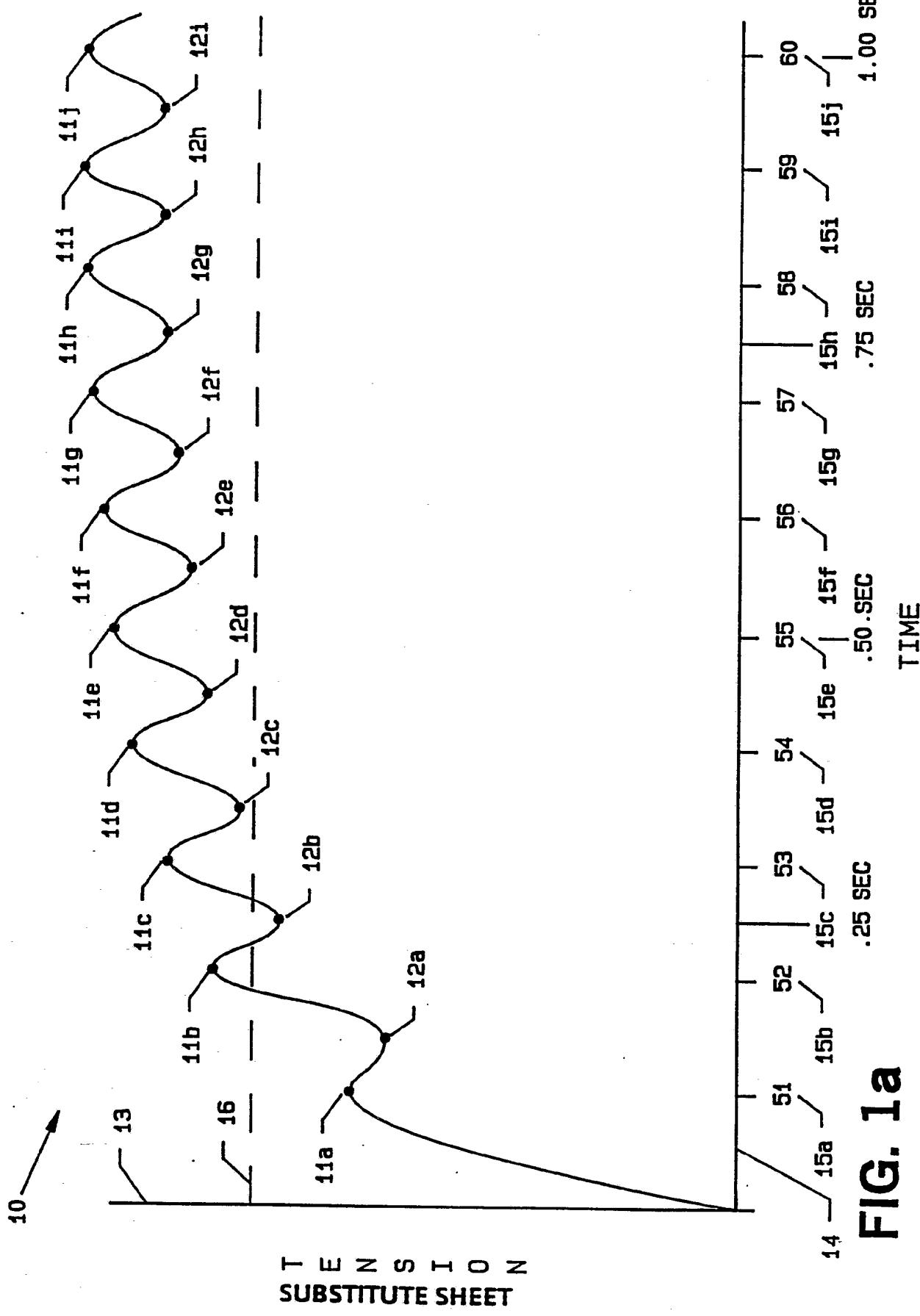
- a. an electrode coupled to muscle tissue of the upper airway of a patient;
- b. means coupled to said electrode for supplying stimulation pulses to said muscle tissue via said electrode;
- c. means coupled to said muscle for sensing tetanic contraction of said muscle tissue; and
- d. means coupled to said sensing means and said supplying means for adjusting said stimulation pulses in response to said supplying means to ensure that said stimulation pulses do not stimulate fused tetanic contraction of said muscle tissue.

10. An apparatus according to claim 9 wherein said adjusting means further comprises means for decreasing the frequency of said simulation pulses.

11. An apparatus according to claims 9 or 10 further comprising a plurality of electrodes coupled to said supplying means.

12. An apparatus according to claims 9, 10 or 11 wherein said adjusting means further comprises means for increasing said frequency of said stimulation pulses.

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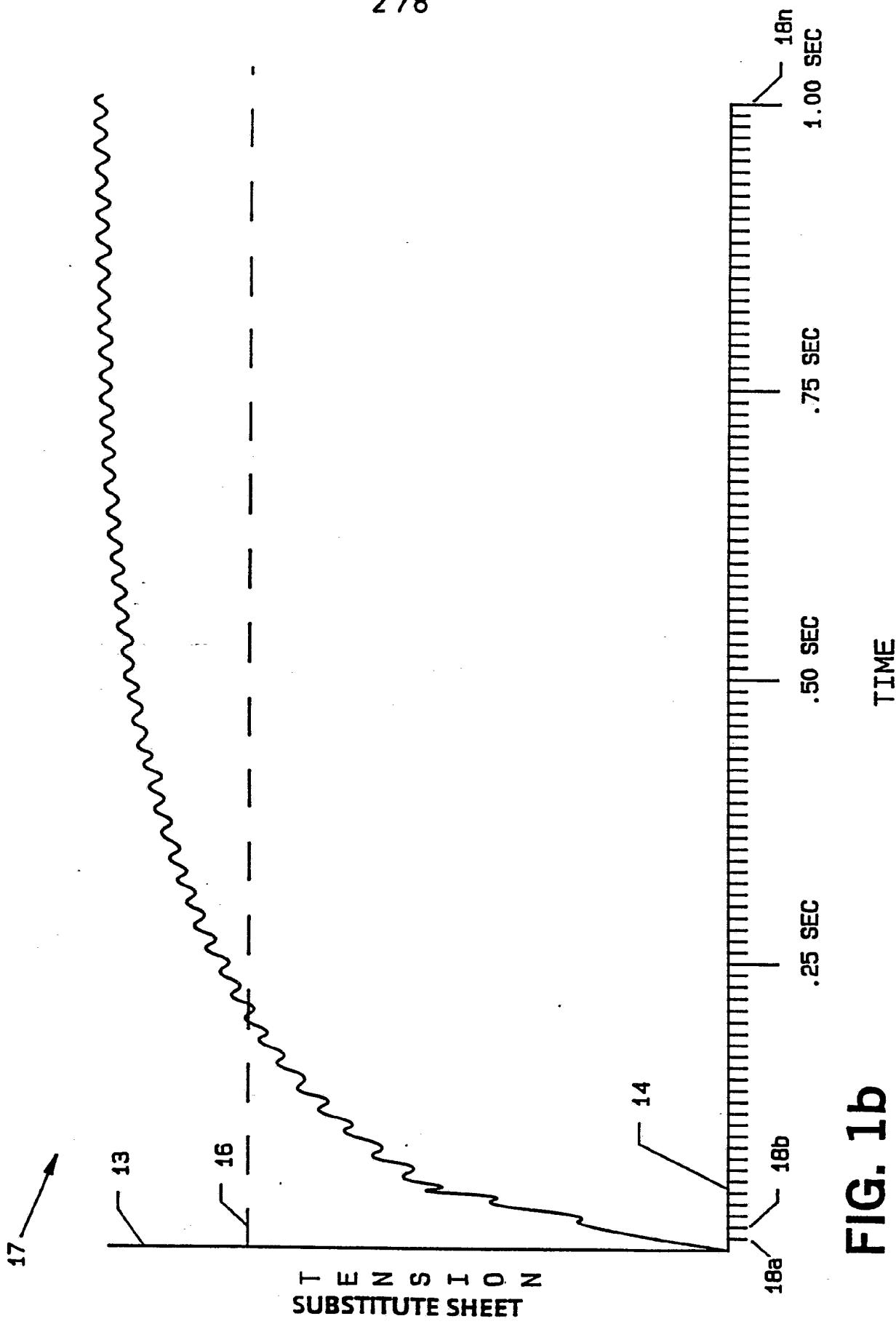
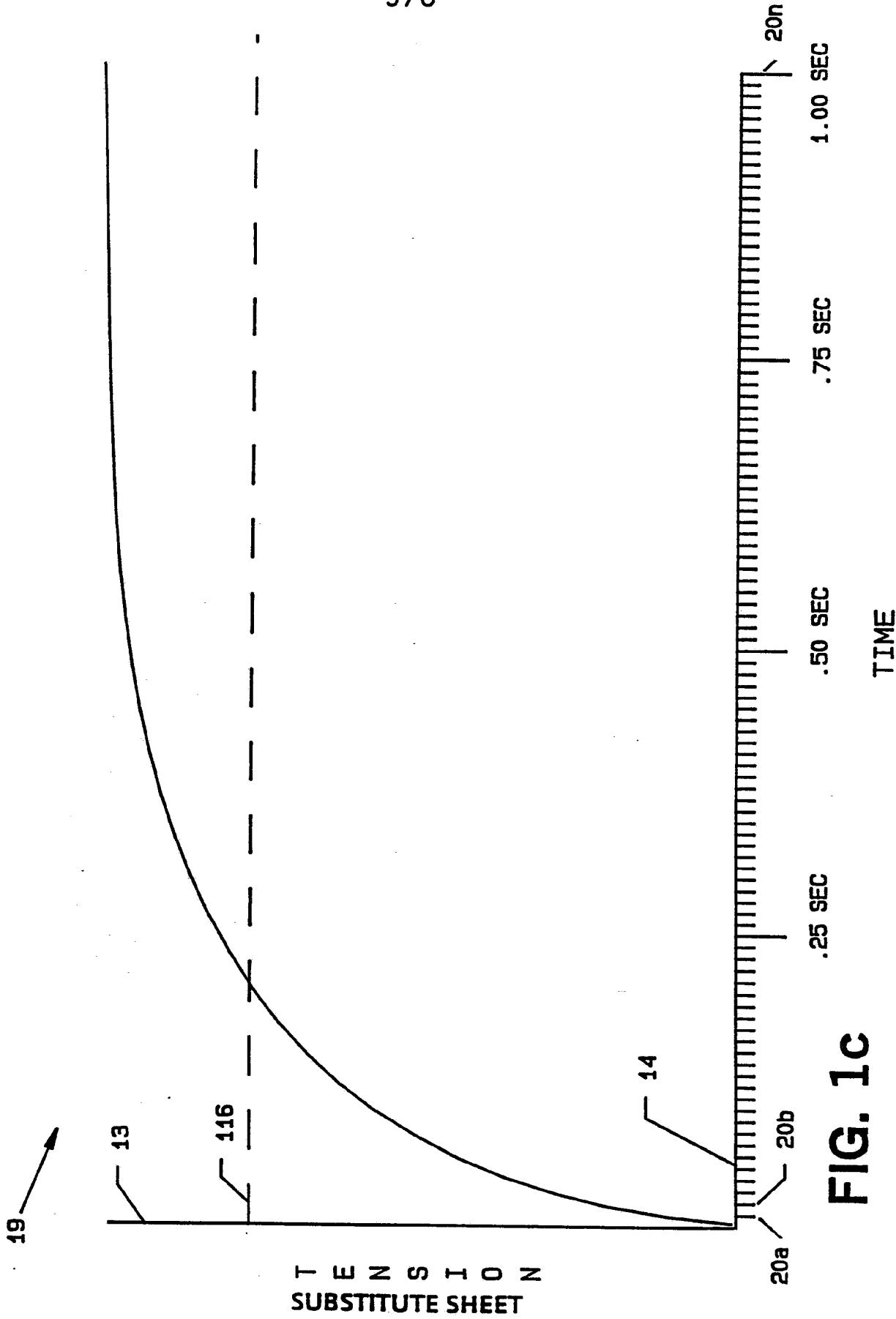


FIG. 1b

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**FIG. 1C**

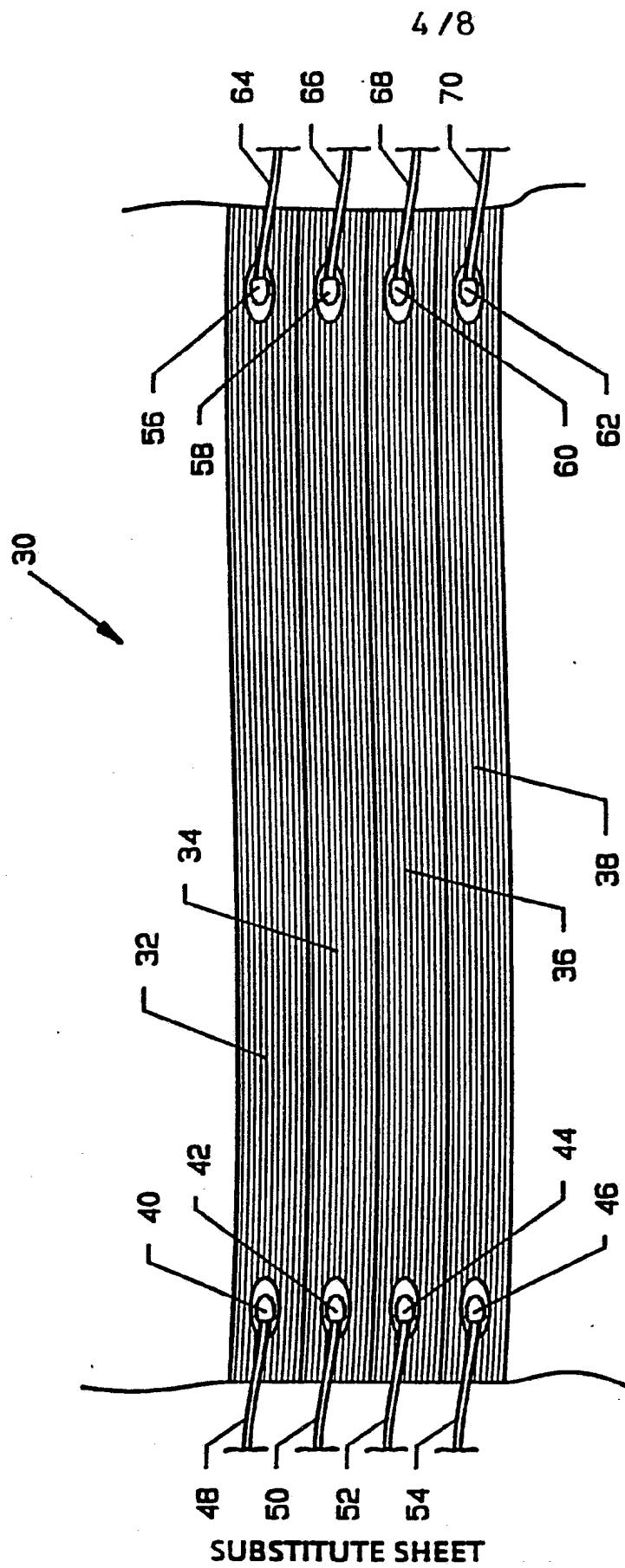
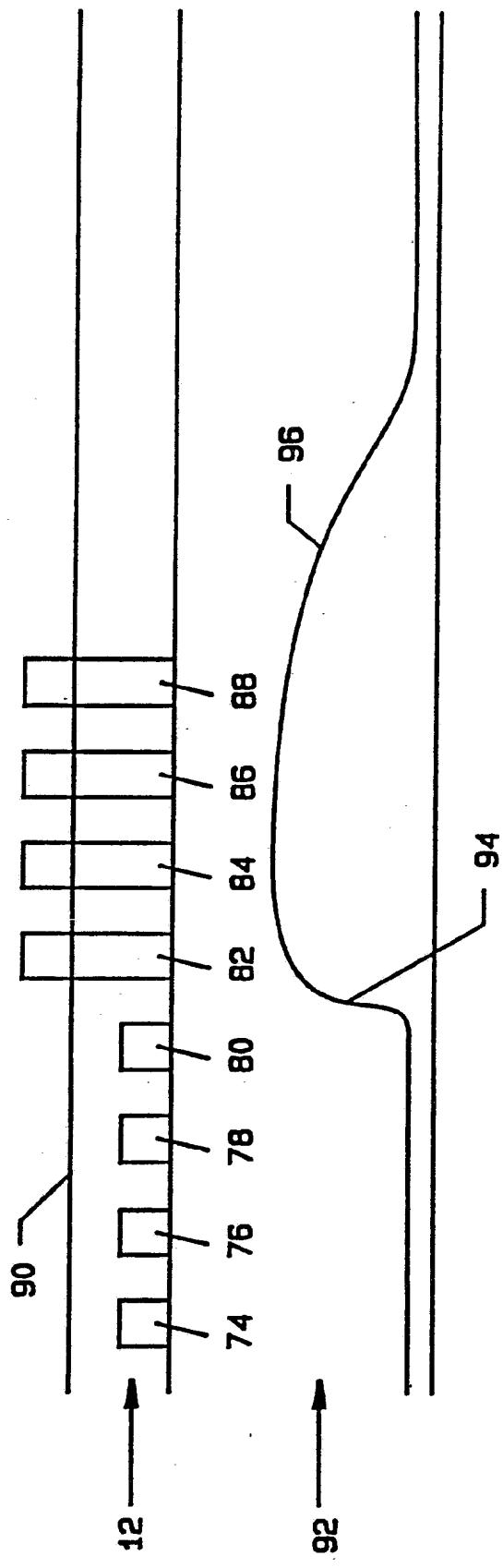
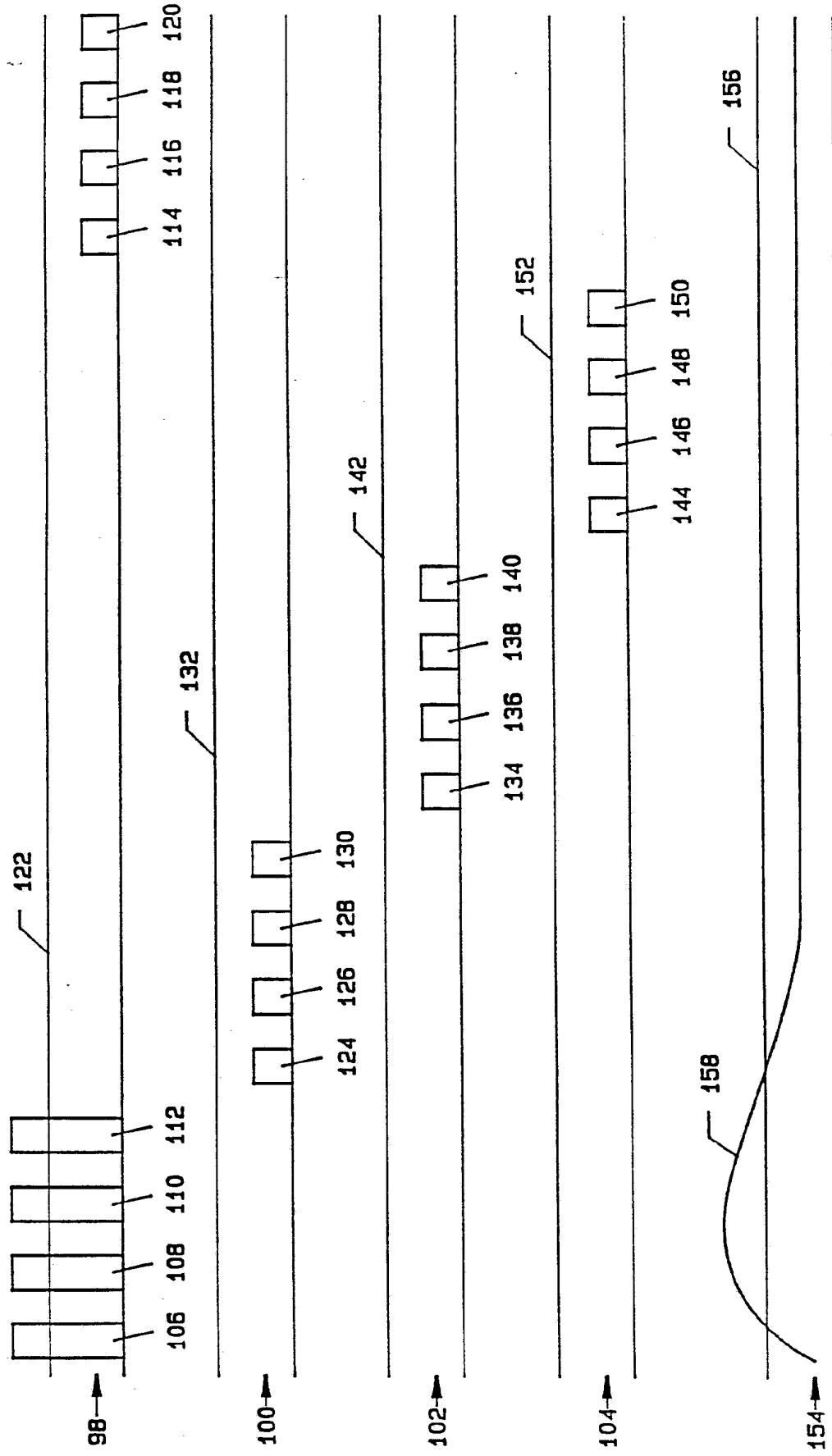


FIG. 2

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**FIG. 3**

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SUBSTITUTE SHEET

FIG. 4

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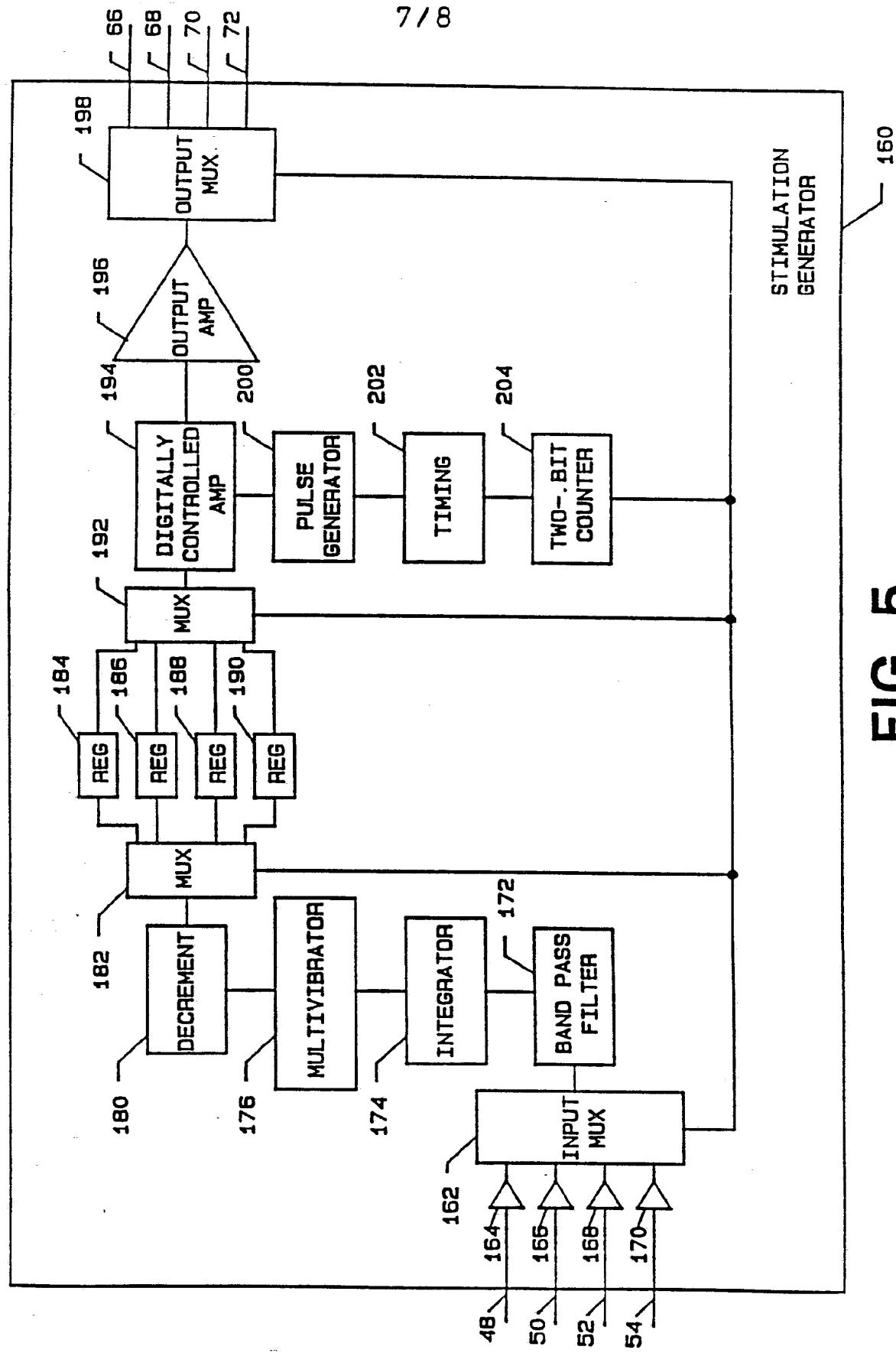


FIG. 5

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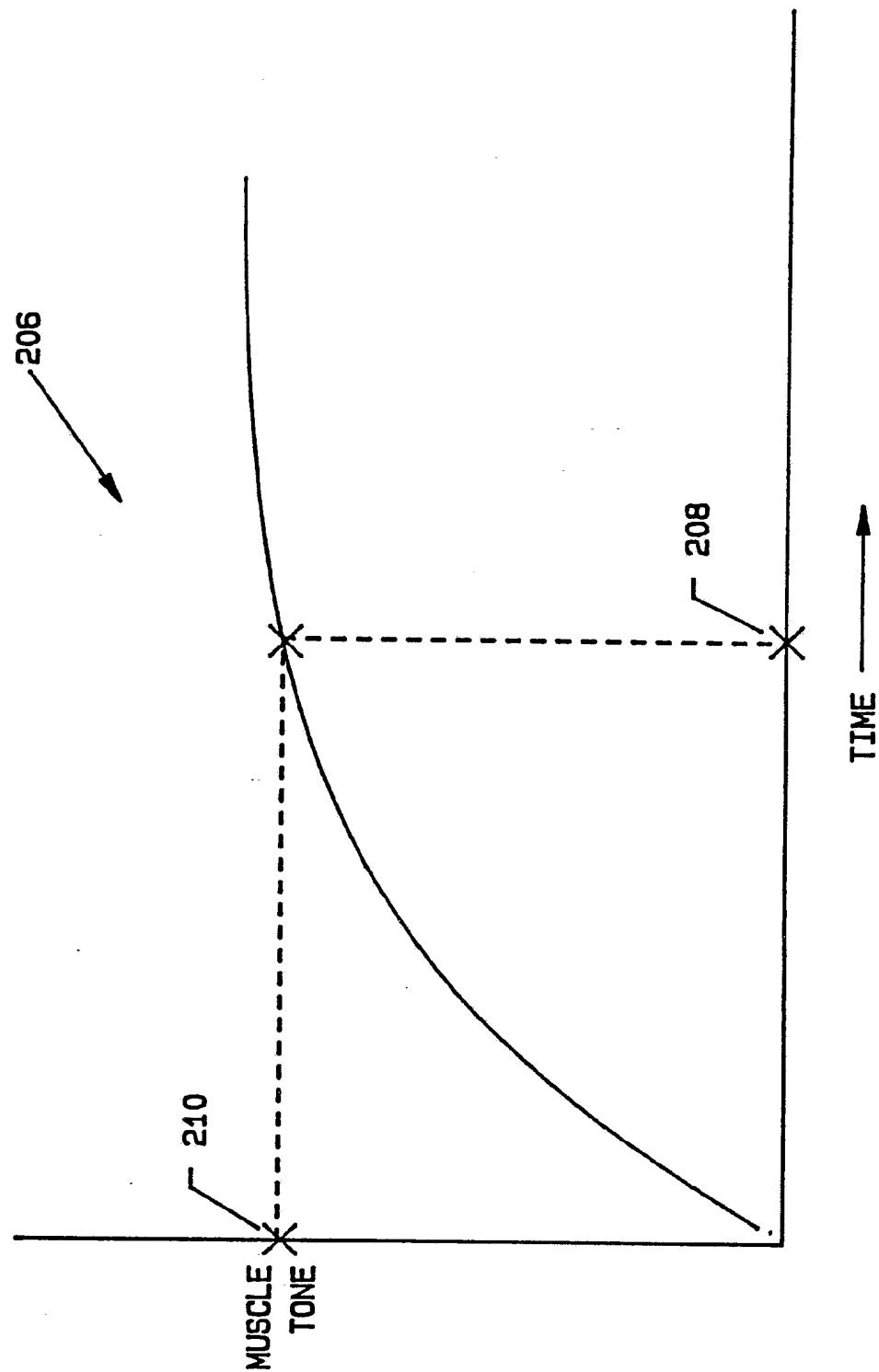


FIG. 6

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 92/02391

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC.

Int.C1. 5 A61N1/36

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1. 5	A61N

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0 036 742 (STIMTECH INC.) 30 September 1981 see abstract ----	3
X	US,A,4 411 268 (J.A.COX) 25 October 1983 see column 2, line 6 - line 35; figure 1 ----	3
A	EP,A,0 404 427 (CHEST CORPORATION) 27 December 1990 see abstract; figures 1-4 ----	3
A	US,A,4 505 275 (W.CHEN) 19 March 1985 see column 10, line 55 - column 12, line 11; figures 5A,5B ----	3 -/-

^o Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 19 OCTOBER 1992	Date of Mailing of this International Search Report 03.11.92
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer HUNT B.W.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	AMERICAN REVIEW OF RESPIRATORY DISEASES vol. 140, 1989, pages 1285 - 1289 H.MIKI ET AL. 'Effects of Submental Electrical Stimulation during Sleep on Upper Airway Patency in Patients with Obstructive Sleep Apnea' cited in the application see the whole document ----	3
A	US,A,4 830 008 (J.A.MEER) 16 May 1989 see the whole document -----	3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/ 02391

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1, 2
because they relate to subject matter not required to be searched by this Authority, namely:
see PCT/Rule: 39.1 (iv)

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9202391
SA 62162**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 19/10/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0036742	30-09-81	US-A-	4294245	13-10-81
		AU-B-	546216	22-08-85
		AU-A-	6856681	01-10-81
US-A-4411268	25-10-83	None		
EP-A-0404427	27-12-90	JP-A-	3023870	31-01-91
US-A-4505275	19-03-85	None		
US-A-4830008	16-05-89	None		